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Pulmonary-Allergy Drugs Advisory Committee Meeting Ivacaftor (Kalydeco) Tablets for oral use sNDA 203188

FDA Opening Remarks and Regulatory History of Ivacaftor Tablets

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October 21, 2014

Overview

- Objective
- Cystic Fibrosis
- Ivacaftor studies that supported previous approvals
- *R117H* mutation in the *CFTR/R117H* clinical program
- Relevant regulatory interactions

Objective

- Discuss sNDA 203188 for ivacaftor oral tablets for the treatment of cystic fibrosis in patients age 6 years and older who have a *R117H* mutation in the *CFTR* gene

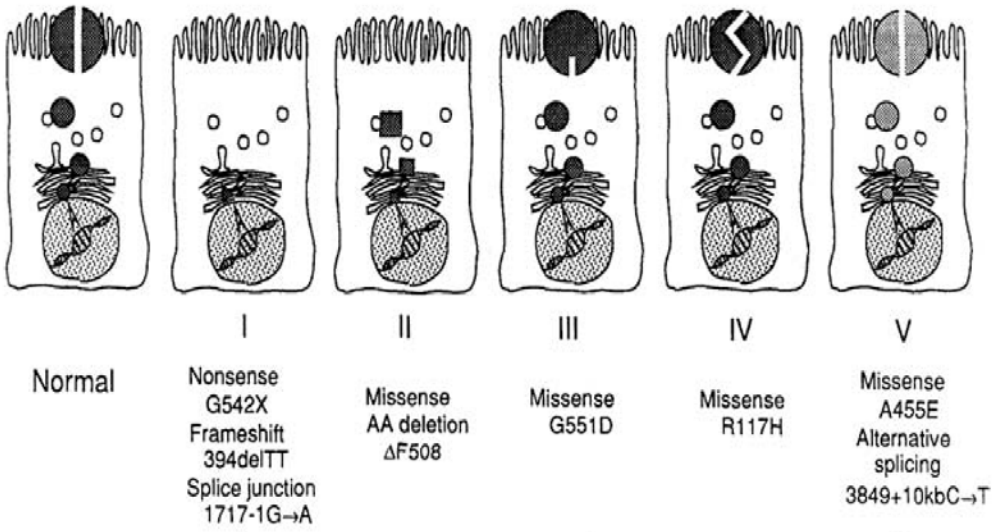
- Safety

- Focus on Efficacy

Cystic Fibrosis (CF)

CF is most common genetic disease in US, ~30,000 people

- Caused by defect in Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), a chloride conducting ion channel
- Autosomal recessive, need presence of 2 CF-causing mutations
- About 2000 known mutations reported in the *CFTR* gene, only a fraction known to be disease causing



[Source: Zielenski J and Lap-Chee T, Ann Rev Genetics, 29:777-807, 1995]

Ivacaftor

Ivacaftor: small molecule ion channel “potentiator”

- Increases chloride transport through the CFTR chloride channel by increasing the “open time”
  - January 2012: approved for CF subpopulation 6 years of age and older defined by presence of *G551D* mutation in the *CFTR* at a dose of 150 mg orally twice daily
  - November 13, 2013: Breakthrough Designation granted for development for other CF subpopulations: those with *CFTR* mutations similar to *G551D* and for subpopulations of CF patients with residual baseline CFTR ion channel function
  - February 2014: sNDA for 8 of 9 subpopulations defined by *CFTR* mutations functionally similar to *G551D* (class III “gating mutations) approved

Efficacy and Pharmacodynamic Endpoint Results Across CF Mutation Subpopulations

			Ivacaftor Treatment Effect				
Study population	**Study Duration**	**N**	**Sweat Chloride mmol/L**	**FEV1 % Predicted**	**CFQ-R Resp points**	**Weight/ BMI**	**Exacerbation**
G551D ≥12yo	48 wk[a]	213	-48 (-51, -45)	10.6% (8.6, 12.6)	8.1 (4.7, 11.4)	+2.8kg (1.8, 3.7)	RR=0.4[b] (0.23, 0.71)
G551D 6-11yo	48 wk[a]	52	-54 (-62, -47)	12.5% (6.6, 18.3)	6.1 (-1.4, 13.5)	+1.9kg (0.9, 2.9)	NA
Other Gating ≥6yo[c]	8wk	39	-49 (-57, -41)	13.8% (9.9, 17.6)	12.8 (6.7, 18.9)	+0.66 kg/m^2 (0.34, 1.32)	NA
F508del ≥12yo	16 wk	112	-2.9 (-5.6, -0.2)	1.7% (-0.6, 4.1)	1.3 (-2.9, 5.6)	-0.16kg (-1.1, -0.7)	NA

a= Primary efficacy was assessed at week 24
b= relative risk of exacerbation
c: includes *G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N*, or *S549R* mutations in the *CFTR* gene
[Sources: Ivacaftor patient labeling; NDA 203-188 Primary clinical review dated Jan 17, 2012 and Primary Statistical Review Jan 13 2012]
FEV=Forced Expiratory Volume
CFQ-R=Cystic Fibrosis Questionnaire-Revised

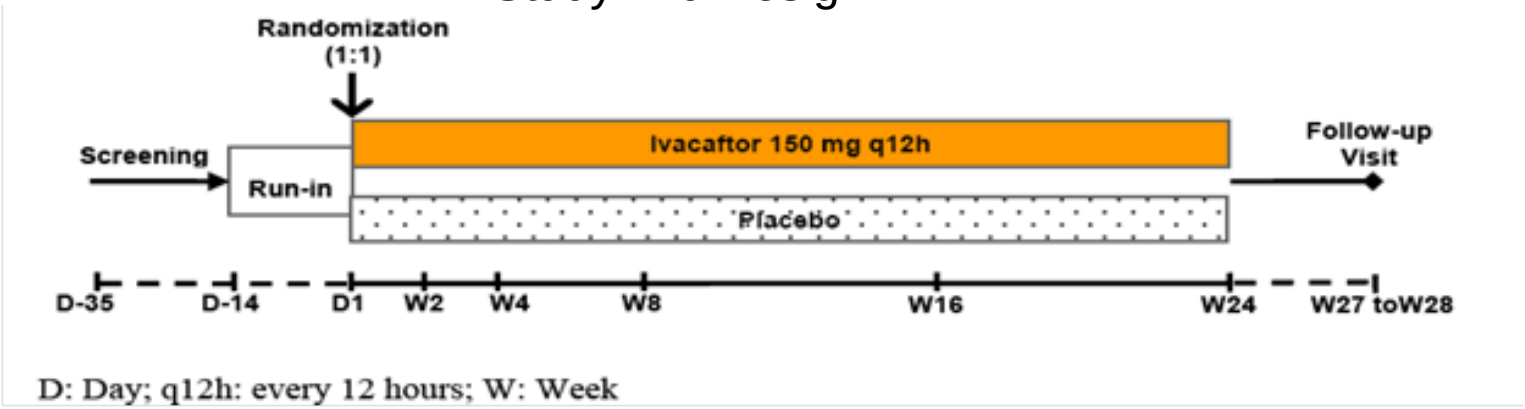
Residual Function Mutations

R117H mutation subpopulation selected to study initially

- Represents a different "class" of mutation in the *CFTR*
  - Conductance defect vs regulation defect
    - CFTR, while defective, is present in the epithelial cell membrane which suggest that CFTR channel may respond to ivacaftor
  - ≈ 3% of CF population (4% for *G551D*)
    - large enough population that a conventional clinical study could be conducted
- Test the hypothesis that ivacaftor would be efficacious in a class of mutations that have some functional differences from those ivacaftor already approved for
  - Given prior demonstration of efficacy in other subpopulations, one study, if robust results, could support approval

R117H Program

Study 110 Design



[Source: Module 5.3.5.1, CSR for Study VX11-770-110, Section 9.1, page 54.]

Primary endpoint:

- Absolute change in % predicted FEV1 through 24 weeks

Secondary endpoints:

- Absolute change in sweat chloride
- Absolute change in CFQ-R respiratory domain
- Absolute change in body mass index (BMI)
- Time to first pulmonary exacerbation

Study 110 Conduct/Analysis

- Enrollment planned for a minimum of 40 and maximum of 80 CF patients ages 6 years and older with a *R117H* mutation in the *CFTR* gene
- Interim analysis for safety and efficacy planned after 40 Pts reached week 8
  - data monitoring committee (DMC) composed of members of the Cystic Fibrosis Foundation Data Safety Monitoring Board
- Enrollment could stop early if a strong treatment effect was observed
- DMC recommended to continue enrollment
  - Enrollment stopped and Study 110 terminated by Vertex
  - 69 pts had been enrolled
    - 8 pts did not complete 24 week treatment period

PRE-NDA Meeting: March 12, 2014

- High level summary data from Study 110 were presented
  - Study 110 failed to meet its primary endpoint, change from baseline compared to placebo in absolute % predicted FEV1 through the 24 week treatment period
  - Secondary endpoints suggest drug activity
    - Decrease in the pharmacodynamic endpoint, sweat chloride,
    - Improvement in respiratory symptoms assess by the CFQR-R respiratory domain
- Additional subpopulation analyses on various subpopulations (age, poly-T status and baseline lung function) showed that adult, those with 5T status, and lower baseline FEV1 appeared to have a better drug response and children a poor response
  - proposed submission of a NDA asking for indication for adult patients with CF and a *R117H* mutation

PRE-NDA Meeting/NDA Submission

- The Division noted that typically such subpopulation analyses are viewed as exploratory
  - Given that there were sufficient patients in the *R117H* mutation CF patient population to be able to study, recommended the conduct of a second clinical trial in the *R117H* mutation subpopulation felt to be most able to respond to treatment to confirm the results of the subpopulation analyses
  - An alternative, albeit viewed as less optimal, would be to submit the full study results and interpretation in a sNDA
- Supplemental NDA submitted on June 30, 2014
  - Proposed indication: “treatment of CF in patients age >18yo who have an *R117H* mutation in the *CFTR* gene”
  - Indication amended on August 19, 2014, to: “treatment of CF in patients age 6 years and older who have an *R117H* mutation in the *CFTR* gene”

Questions for Discussion and Voting

- Total of 5 questions
- Questions 2, 4, and 5 require voting
- Questions 1 and 3 are discussion only

Thank you

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Review of Efficacy

Thomas Permutt
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21 October 2014

Study 110

- Failed on primary analysis
- Primary analysis important because …
  - Prespecification controls probability of approving completely ineffective drug
  - This would be a bad error
  - Strict control is not possible post hoc

Inferential problem is different here

- Ivacaftor already found effective in some patients
- In what other patients is it effective?
  - There will be many subgroups
  - Some of them will be small
- Many types of error
  - Say it's effective in all subgroups when it is ineffective in all
  - Say it's effective in a subgroup when it isn't
  - Say it isn't effective in a subgroup when it is
- Prespecification of primary analysis cannot control probabilities of all these types of error

Example: two subgroups, possibly different

- Do separate studies
  - Control type I and type II error rates within studies
    - But not across studies
  - Need enough patients to make reliable inference within each group
- Do one study, assume effects the same
  - Need fewer patients overall
  - If groups really are different, error is inevitable
    - Positive overall finding is wrong for one group
    - Negative overall finding is wrong for the other group
  - Do this but look at subgroups post hoc
    - Required by regulation for age, race, sex

What do we have?

- Study 110
  - Nominally significant positive effect on lung function in adults
  - Plausible but inexplicably strong negative effect in children
  - Positive effects on sweat chloride in both adults and children
- Study 112
  - Uncontrolled
  - Relapse on withdrawal of active drug
  - Favorable change in both groups on initiation or resumption of active drug

Age or other explainer?

- Confounding of age with baseline function, poly-T
- Separate analyses by age, baseline, poly-T not very useful
- Even multiple regression not highly reliable, but …

Term	Estimate	Std Error	t Ratio	P-Value
Intercept	0.95	0.99	0.96	0.34
Ivacaftor	-0.78	0.99	-0.79	0.43
>18	-0.73	1.51	-0.48	0.63
5T	0.93	1.00	0.93	0.36
Baseline <70%	1.44	1.65	0.87	0.39
Baseline 70% to 90%	0.49	1.29	0.38	0.71
>18*Ivacaftor	4.10	1.52	2.71	0.01
5T*Ivacaftor	0.68	1.00	0.68	0.50
Baseline <70%*Ivacaftor	-1.78	1.65	-1.08	0.29
Baseline 70% to 90%*Ivacaftor	-1.07	1.29	-0.83	0.41

- Age nominally significant even controlling for baseline, poly-T
- Baseline and poly-T not significant controlling for age

Summary

- Prespecified analysis insufficient, post hoc analysis necessary
- Study 110
  - Nominally significant effect on lung function in adults
  - Unexplained negative effect in children
  - Positive effect on sweat chloride in both adults and children
- Study 112
  - Changes in right direction on discontinuation and resumption or initiation

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Clinical Considerations for Efficacy and Summary of Safety

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October 21, 2014

Overview

- Efficacy results for Study 110 including relevant subpopulation analyses
- Supportive efficacy information from Study 110 and open-label roll-over (Study 112)
- Summary of efficacy
  - Main outcomes
  - Subpopulation-based outcomes
- Dilemma subpopulation analyses present
- Main issue for discussion

Overall Efficacy

	Change through Week 24					
	% Predicted FEV1 (%)		Sweat Chloride (mmol/L)		CFQ-R respiratory (points)	
Study Drug	n	Difference (95%CI)	n	Difference (95%CI)	n	Difference (95%CI)
Placebo	35	2.1	35	-24	34	8.4
Ivacaftor	34	(-1.1, 5.4)	32	(-28, -20)	33	(2.2, 14.6)

*MMRM analysis with treatment, age, week, baseline value, treatment by week, and subject as a random effect
Source: FDA Statistician

No significant difference in BMI or time to first exacerbation

Subpopulation Analysis: Age

		Change through Week 24					
		% Predicted FEV1 (%)		Sweat Chloride (mmol/L)		CFQ-R respiratory (points)	
Age	Study Drug	n	Difference (95%CI)	n	Difference (95%CI)	n	Difference (95%CI)
6 to 11	Placebo Ivacaftor	8 9	-6.3 (-12.00, -0.71)	8 8	-28 (-37, -18)	7 8	-6.1 (-15.7, 3.4)
12-17	Placebo Ivacaftor	1 1	---		---		---
≥18	Placebo Ivacaftor	26 24	5.0 (1.2, 8.8)	26 22	-22 (-27, -17)	26 24	12.6 (5.0, 20.3)

*MMRM analysis with treatment, age, week, baseline value, treatment by week, and subject as a random effect
Source: FDA Statistician

Subpopulation Analysis: Poly-T Status

		Change through Week 24					
		% Predicted FEV1 (%)		Sweat Chloride (mmol/L)		CFQ-R respiratory (points)	
Poly-T Status[a]	Study Drug	n	Difference (95%CI)	n	Difference (95%CI)	n	Difference (95%CI)
5T	Placebo Ivacaftor	24 14	5.3 (1.3, 9.3)	24 13	-24 (-30, -18)	24 14	15.3 (7.7, 22.9)
7T	Placebo Ivacaftor	5 11	0.2 (-8.1, 8.5)	5 10	-24 (-34, -14)	5 11	5.2 (-12.9, 23.4)

a= Confirmed poly-T tract data
*MMRM analysis with treatment, age, week, baseline value, treatment by week, and subject as a random effect
Source: FDA Statistician

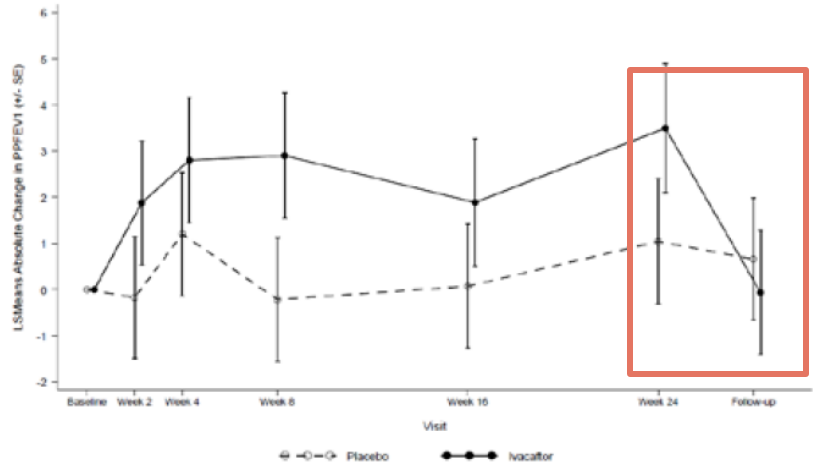
Subpopulation Analysis: Baseline FEV1

		Change through Week 24					
		% Predicted FEV1 (%)		Sweat Chloride (mmol/L)		CFQ-R respiratory (points)	
Baseline FEV1 value	Study Drug	n	Difference (95%CI)	n	Difference (95%CI)	n	Difference (95%CI)
<70%	Placebo Ivacaftor	15 13	4.0 (-2.1, 10.2)	15 12	-26 (-32, -19)	15 13	11.4 (1.2, 21.6)
≥70 to ≤90%	Placebo Ivacaftor	14 14	2.6 (-2.3, 7.5)	14 14	-20 (-27, -13)	13 14	8.8 (-2.6, 20.2)
>90%	Placebo Ivacaftor	6 7	-4.3 (-9.9, 1.3)	6 6	-27 (-40, -14)	6 6	-0.7 (-10.4, 9.0)

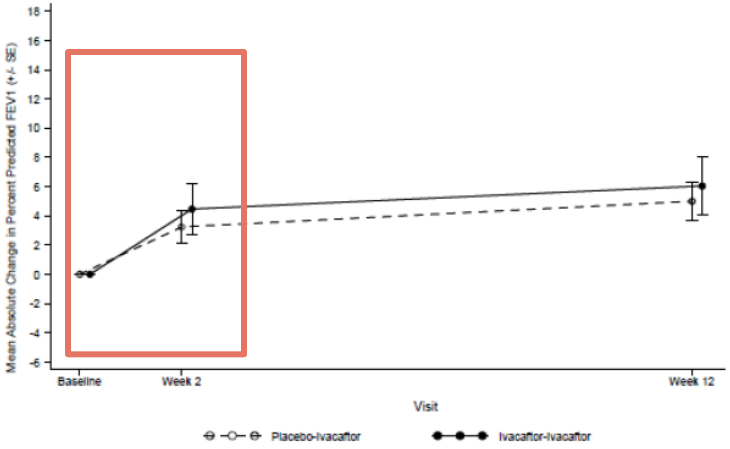
*MMRM analysis with treatment, age, week, baseline value, treatment by week, and subject as a random effect
Source: FDA Statistician

Supportive Analysis: Washout/Restart (FEV1)

A Study 110



B Study 112



[Source: A: Figure 14.2.1.3 Study 110 CSR, p. 1544 of 2633; B: Figure 4.1 Study 112 Week 12 interim analysis, p. 21 of 173]

Main Outcomes: Overall Population

- FEV1
  - Study 110 did not meet its primary endpoint, change in FEV1 compared to placebo through 24 weeks of treatment (2% difference from placebo).
- CFQ-R respiratory domain
  - Mean change in CFQ-R demonstrated a significant treatment benefit for ivacaftor (difference of 8.4)
- Sweat Chloride
  - Mean decrease in sweat chloride was significant (-24 mmol/L) in patients treated with ivacaftor

No difference in BMI or exacerbations between ivacaftor and placebo treatment groups.

Efficacy and Pharmacodynamic Endpoint Results Across CF Mutation Subpopulations

			Ivacaftor Treatment Effect				
Study population	**Study Duration**	**N**	**Sweat Chloride mmol/L**	**FEV1 % Predicted**	**CFQ-R Resp points**	**Weight/ BMI**	**Exacerbation**
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F508del ≥12yo	16 wk	112	-2.9 (-5.6, -0.2)	1.7% (-0.6, 4.1)	1.3 (-2.9, 5.6)	-0.16kg (-1.1, -0.7)	NA
R117H 6-11yo	24 wk	69	-24 (-28, -20)	2.1 (-1.1, 5.4)	8.4 (2.2, 14.6)	+0.26 kg/m^2 (-1,6, 2.1)	HR = 0.93[c]

a= Primary efficacy was assessed at Week 24
b= relative risk of exacerbation
c= time-to-first exacerbation, hazard ratio
d: includes *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, or *S549R* mutations in the *CFTR* gene
[Sources: Ivacaftor patient labeling; NDA 203-188 Primary clinical review dated Jan 17, 2012 and Primary Statistical Review Jan 13 2012, FDA statistical analyses]

Subpopulation Analyses

- Based on age:
  - Improvement in FEV1 (5% predicted) and CFQ-R (12.6 points) for the adult population
  - A 6% decrease in FEV1 in children 6-11 years of age
- Based on poly-T tract:
  - Improvement in FEV1 (5% predicted) and improvement in CFQ-R (15.3 points) in patients with confirmed 5T poly-T status
  - No improvement in FEV1 in patients with 7T poly-T status
- Based on lung function:
  - Improvement in FEV1 of 4.0% predicted in patients with baseline FEV1 of <70%, 2.6% in patients with baseline 70-90%, and a decrease of 4.3% in patients with baseline FEV1 >90%
  - Improvement in CFQ-R of 11.4 and 8.8 in patients with baseline FEV1 of <70% and 70-90% predicted, respectively

All subpopulations demonstrated a significant reduction in sweat chloride with ivacaftor treatment.

Dilemma

Can a single subpopulation adequately define the patient population that may benefit from ivacaftor?

- Age
  - Adult patients appear to benefit more
    - Is benefit based on worse lung function in adults?
  - Children 6-11 yrs on ivacaftor have a decrease FEV1
    - Not consistent with current experience with other CFTR mutation-based subpopulations
- Poly-T
  - 5T population seems to benefit more
    - Is benefit based on worse lung function in 5T patients?
    - Some 7T pts benefit
- FEV1
  - Pts with worse lung function may benefit more
    - Not consistent with current experience
    - What is the cut-off?

Main Issue

While post hoc analyses are generally considered hypothesis-generating, given what we know about the disease, how ivacaftor works, and the efficacy previously demonstrated in different *CFTR* mutation-based CF patient subpopulations, has substantial evidence of efficacy been shown for ivacaftor in CF patients with a *R117H* mutation in the *CFTR*?

Summary of Safety

Safety profile of ivacaftor in patients with CF is primarily from placebo-controlled data from clinical trials in approximately 350 CF patients

- Two 48-week trials in patients with *G551D* mutation
- One 16-week trial in patients with *F508* mutation
- Open label safety data from CF patients exposed to ivacaftor for as many as 144 weeks.

- Two and five percent of patients treated with ivacaftor and placebo, respectively, discontinued due to adverse reactions
- SAEs, that occurred more frequently in ivacaftor treated patients: abdominal pain, increased hepatic enzymes, and hypoglycemia
  - Two patients on ivacaftor were reported to have transaminase-related serious adverse reactions vs 0 for placebo
  - Two patients on placebo and 1 patient ivacaftor discontinued treatment for elevated transaminases, all >8 x ULN

Common Adverse Reactions in CF Patients with a *G551D* Mutation and > Placebo in 48-week Trials

	Incidence: Pooled 48-week Trials	
Adverse Reaction (Preferred Term)	**KALYDECO N=109 n (%)**	**Placebo N=104 n (%)**
Headache	26 (24)	17 (16)
Oropharyngeal pain	24 (22)	19 (18)
Upper respiratory tract infection	24 (22)	14 (14)
Nasal congestion	22 (20)	16 (15)
Abdominal pain	17 (16)	13 (13)
Nasopharyngitis	16 (15)	12 (12)
Diarrhea	14 (13)	10 (10)
Rash	14 (13)	7 (7)
Nausea	13 (12)	11 (11)
Dizziness	10 (9)	1 (1)

[Source: Kalydeco approved labeling]

Safety: Study 110

- No deaths reported, 10 SAEs, 6 and 4, for the placebo and ivacaftor groups, respectively over the 24-week treatment period.
  - most common SAE was CF exacerbation, with 6 and 3 reported in the placebo and ivacaftor treatment groups, respectively.
- Common adverse events for both treatment groups were consistent with those commonly observed in the CF population
- No substantial differences between ivacaftor and placebo-treated patients in the number or severity of patients who reported elevated transaminases.
- The potential for cataracts in children was identified in the ivacaftor program after initial approval in the *G551D* mutation subpopulation, on the basis of nonclinical findings of lens opacities in juvenile rat studies.
  - there were no clinically relevant changes in ophthalmologic exams, and no reports of cataract development.

Safety Conclusion

- Safety data for Study 110 and open-label rollover (Study 112) do not reveal any new safety concerns
  - There is no reason to expect that the safety profile would be different in CF patients with a *R117H* mutation compared to CF patients with *G551D*, *F508*, or other mutation-based subpopulations for which ivacaftor is approved or has been studied
  - No new data that raised concerns over increased liver transaminases or other liver injury in patients receiving ivacaftor.
  - There were no reports of CF patients developing cataracts/lens opacities during Study 110
    - 24 weeks is a relatively short evaluation period for cataracts and evaluations continue.

Thank you

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Charge to the Committee

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Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
October 21, 2014

Approval of an Application -21 CFR 314.105 (c)

"FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling"

Efficacy Standard
-21 CFR 314.125 Refusal to Approve an Application

(b) (5) "… substantial evidence consisting of adequate and well-controlled investigations … that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."

Efficacy Standard
-21 CFR 314.125 Refusal to Approve an Application

(b) (2) "… do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

(b) (3) "The results of the test show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions."

(b) (4) "There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

Questions for Discussion and Voting

- Total of 5 questions
- Questions 2, 4, and 5 require voting
- Questions 1 and 3 are discussion only

Question 1
(Discussion Question)

Discuss the efficacy data for ivacaftor oral tablets 150 mg twice daily to support the proposed indication for treatment of cystic fibrosis in patients age 6 years and older who have a *R117H* mutation in the *CFTR* gene. Consider the following issues in the discussion: primary analyses, subgroup analyses based upon age, baseline FEV1, and poly-T status, the impact of the known mechanism of action of ivacaftor and the demonstrated efficacy in other CF subpopulations on interpretation of *R117H* mutation efficacy data.

Question 2
(Voting Question)

Do the efficacy data provide substantial evidence of a clinically meaningful benefit for ivacaftor oral tablets 150 mg twice daily for the treatment of cystic fibrosis in patients age 6 years and older who have a *R117H* mutation in the *CFTR* gene?

If not, what further data should be obtained?

Question 3
(Discussion Question)

Discuss the safety data for ivacaftor oral tablets 150 mg twice daily.

Question 4
(Voting Question)

Are the safety data from the overall ivacaftor cystic fibrosis program sufficient for approval of ivacaftor 150 mg twice daily for the treatment of cystic fibrosis in patients age 6 years and older who have a *R117H* mutation in the *CFTR* gene?

If not, what further data should be obtained?

Question 5
(Voting Question)

Do the data support approval of ivacaftor oral tablets 150 mg twice daily for the treatment of cystic fibrosis in patients age 6 years and older who have a *R117H* mutation in the *CFTR* gene?

If not, what further data should be obtained?

Thank You